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Original article

Neonatal cardiomyopathy: a 20-year overview of a reference centre

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Abstract

Background: Cardiomyopathies (CMs) are rare multifactorial diseases of the heart muscle. Neonatal forms present as a myocardial injury in the absence of primary valvular, great vessels or septal anomalies. Despite being uncommon diseases, CMs may lead to potentially severe sequelae and considerable risk of neonatal death. This study aimed to provide an overview of neonatal CM (NCM) and describe its aetiology, initial clinical findings, morbidity and mortality.

Methods: Retrospective observational study of all newborns diagnosed with CM admitted to the Neonatal Intensive Care Unit (NICU) of Centro Hospitalar Universitário de S. João, in Porto, Portugal, between 1997 and 2017. Data collected included demographic and perinatal information, clinical presentation, CM type and aetiology, treatments, complications and outcome.

Results: Twenty-eight newborns with CM diagnosis were selected: 26 neonates were considered to have primary CM forms and 2 secondary CMs. Of those 26 diagnosed with primary CMs, 16 had hypertrophic CM, 8 had dilated CM, and 2 had tachycardia-induced CM. Secondary CMs comprehended 1 case of infiltrative CM and another of CM due to corticosteroids toxicity. Cardiac murmur (57.1%) was the most common finding, followed by heart failure (HF, 28.6%), cyanosis (21.4%), arrhythmia and sepsis (17.9%, each), and hypertension (10.7%). Two newborns were placed on a heart transplant waiting list. Three neonates developed congestive HF and 1 had a sudden cardiac death event. A total of 4 (14.3%) newborns have deceased during the NICU stay. More than 90% of the neonates were prescribed more than one medicine at discharge.

Conclusion: NCMs require critical intensive care management. Unspecific symptoms characterise clinical findings. The majority of

newborns have idiopathic primary CMs, but rare heterogeneous aetiologies may be the underlying cause in some cases. Thus, a multidisciplinary approach is mandatory.

Keywords

Cardiomyopathies, newborn, Neonatal Intensive Care Unit, aetiology, clinical presentation, outcome.

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Introduction

Cardiomyopathies (CMs) are rare multifactorial diseases of the heart that present as heterogeneous phenotypes structurally and functionally, despite the systematic association with cardiac dysfunction [1].

According to the American Heart Association (AHA), CMs can be classified as primary if caused by intrinsic factors such as genetic abnormalities and predominantly affecting the cardiac muscle, or secondary if precipitated by extrinsic factors like drugs, nutritional deficiencies, infiltrative disorders or metabolic diseases and generally presenting with systemic manifestations of other organs [2]. Both forms are regularly diagnosed in children [1].

Primary CMs can be further divided into genetic, mixed (genetic and mostly nongenetic) or acquired, and generally are a diagnosis of exclusion [3]. Genetic CMs comprehend hypertrophic CM (HCM), arrhythmogenic right ventricular CM/dysplasia, left ventricular noncompaction, conduction system disease and ion channelopathies. Mixed CMs encompass dilated CM (DCM) and primary restrictive nonhypertrophied CM. Acquired CMs include myocarditis/inflammatory CM, stress ("Tako-Tsubo") CM, peripartum CM, tachycardia-induced CM (Tachy-CM) and CM in infants of insulin-dependent diabetic mothers [2].

Secondary CMs can emerge in the context of infiltrative diseases such as Hurler's disease, endocrine pathologies like diabetes mellitus and autoimmune disorders, namely systemic lupus erythematosus, among others [2].

Although there is a wide variety of phenotypical presentations [4], primary forms of CMs are the majority of diagnosis in children [1, 5]. HCM and DCM are both primary CMs associated with adverse outcomes [5]. Indubitably, CMs are one of the leading causes of morbimortality in children and neonates [5-7] and, along with myocarditis, are important triggers to end-stage heart failure (HF), being held liable for more than 50% of all pediatric heart transplants [1, 7]. Moreover, almost 40% of all infants with symptomatic CM at presentation require heart transplantation or ultimately die of the condition within 2 years [8, 9]. The percentage of children with CM who receive a heart transplant has not declined over the past 10 years [9, 10].

CM's aetiological identification is crucial to guarantee and plan an optimal medical treatment, predict arising of common complications and infer prognosis [11].

Fetal CM is a rare entity, associated with poor prognosis [12]. Furthermore, it represents up to 11% of all cardiac diseases diagnosed *in utero* [12].

Neonatal CMs (NCMs) are rare conditions of the neonate's heart muscle in which there is a myocardial injury in the absence of primary valvular, great vessels or septal anomalies [13]. Their diagnosis demands a high level of clinical suspicion [4]. Also, the assessment of such patients requires a systematic approach, frequently involving not just the examination by neonatology and cardiology experts, but metabolic and genetic analysis as well [14]. Neonatal presentation of CMs is often the most severe [14]. Notwithstanding its low prevalence, accounting for about 1% of infant heart diseases [13-15], NCMs are responsible for 10% of all pediatric cardiac deaths [13, 15]. Hence, potentially severe sequelae and considerable risk of death [11] should be taken into consideration when treating these pathologies.

Medical therapy has a limited role in the treatment and prognosis of NCMs [4]. Therapeutic interventions are primarily used to relieve symptoms [4, 13, 15, 16], prevent disease progression as well as possible complications [13], and prolong survival [15]. Efficient medical treatment for CM is yet to be discovered, regardless of the successful advances in the medical management of several congenital heart diseases [9]. Nonetheless, both morbidity and

mortality have substantially decreased as a result of medical breakthroughs [13].

This study aimed to provide an overview and describe aetiology, initial clinical findings, morbidity and mortality of all cases of NCM that were identified at or referred to a level III Neonatal Intensive Care Unit (NICU), in Porto, Portugal.

Patients and methods

We conducted an observational retrospective study of all patients diagnosed with CM at or referred to the NICU, a tertiary unit with an average of 400 admissions per year and 17 beds, at Centro Hospitalar Universitário de S. João (CHUSJ). This study focused on patients admitted between January 1, 1997, and December 31, 2017, with 28 days or less of age at diagnosis.

One researcher collected all data compatible with suspicion of either CM or myocarditis from the newborns' medical records and the CHUSJ's neonatal electronic clinical database.

The following data was collected: demographic information (date of birth and sex); pregnancy information (pregnancy vigilance and complications during pregnancy); birth information (birth delivery; gestational age; 1st , 5th and 10th minute Apgar scores; need for neonatal reanimation with endotracheal tube [ETT]; weight at birth [in grams]; length at birth [in centimeters] and head circumference at birth [in centimeters]); parental information (maternal illness and parental consanguinity); pathology related information (type and aetiology of CM; age at diagnosis [in days]; family history of thromboembolic events, sudden cardiac death [SCD] before 30-35 years of age, inherited metabolic disease and muscular dystrophy); clinical presentation (HF, acute pulmonary oedema, arrhythmia, arterial hypertension, cardiac murmur, cyanosis and sepsis); prior prenatal exposure to corticoids; cardiopulmonary information (left ventricular hypertrophy; left atrial enlargement; pulmonary hypertension; need for invasive mechanical ventilation [IMV]; days of mechanical ventilation); cardiovascular medication (acute and long-term management – inotropic agents, diuretics, afterload-reducing agents, preload- and afterload-reducing agents, vasopressors, angiotensin-converting enzyme inhibitors [ACEIs], beta-blockers and digoxin; general management – anticoagulation and amiodarone); heart transplantation; complications (congestive HF; arrhythmia; SCD and thromboembolic events); hospital admission information (entry date in the hospital; age at entry date [in days] and reason for hospital admission); hospital discharge information (age at discharge date [in days]; weight at discharge date [in grams]; length at discharge date [in centimeters]; head circumference at discharge date [in centimeters]; length of hospital stay [in days]; clinical state at discharge; prescribed medication at discharge and destination).

Later, we analysed clinical information from pediatric cardiology records as well as laboratory findings and imaging reports during hospitalisation at the NICU. That analysis allowed the assessment of which patients corresponded to actual cases of CM and which had other diagnoses subsequently established. Initial data collection identified 37 newborns with a clinical presentation that raised the suspicion of possible underlying CM. Nine cases were excluded since the suspected diagnosis of CM was not confirmed. Therefore, in total, 28 newborns were selected.

Fetal CM diagnosis was validated according to the criteria considered by Ezon et al. [12]. CM's diagnosis in newborns was verified in the presence of suggestive clinical history and thorough physical examination when evaluated by a pediatric cardiologist and following confirmation by compatible echocardiographic findings [4]. CMs' type and aetiology were defined as stated by the AHA classification [2].

Local ethics-committee approval was obtained.

Data collected were recorded in a digital database (Statistical Package for the Social Sciences – SPSS® 25).

Results

Type of cardiomyopathy

Through analysis of clinical and imagiologic evolution during the NICU stay, we found that all 28 newborns presented with CMs. **Fig. 1** summarises data regarding neonates' CM aetiology. Twenty-six (92.9%) newborns were considered to have primary CM forms and 2 (7.1%) secondary CMs. Of those 26 diagnosed with primary CMs, 16 (57.1%) had HCM, 8 (28.6%) had DCM, and 2 (7.1%) had Tachy-CM. Secondary CMs comprehended 1 (3.6%) newborn with infiltrative CM, specifically DCM in the context of severe Mucopolysaccharidosis type 1 (Hurler's Syndrome), and another (3.6%) newborn

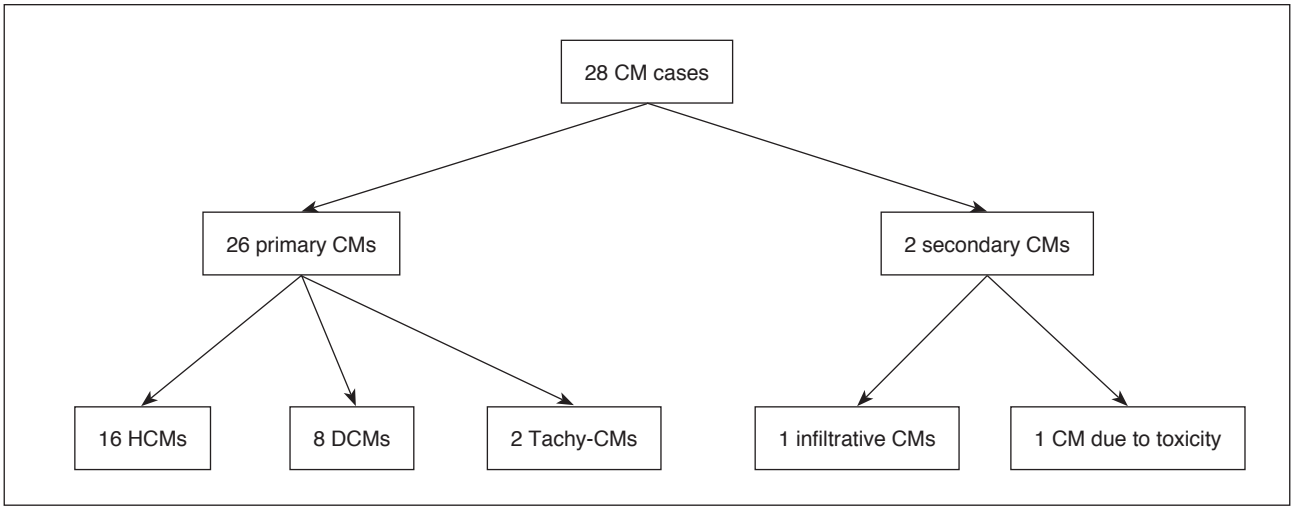

Figure 1. Flow chart of the study population.
CM: cardiomyopathy; HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; Tachy-CM: tachycardia-induced cardiomyopathy.

with CM due to toxicity, particularly an HCM secondary to corticosteroids (CCTs).

Diagnosis and perinatal clinical information

Diagnosis of CM was established prenatally in 2 newborns and during the neonatal period in the remaining 26. The average age at diagnosis was 8.5 days (range 1-26 days). A quarter of all pregnancies, including 1 twin pregnancy, resulted in premature births. The mean gestational age was 37 weeks (range 32-41 weeks), and newborns' birth weight was on average 3,301 grams (range 2,150-5,200 grams). 60.7% of the newborns were male and 39.3% female. Three patients needed neonatal reanimation with EET. Additionally, we identified 3 cases of prior prenatal exposure to corticoids.

Family history

Only 3 newborns had a family history of CM. Two of them had a history of SCD before 30-35 years old, and 1 had an older brother who died from myocarditis.

Clinical presentation

Neonates' clinical presentation of CM was varied with overlapping signs (**Tab. 1**). Cardiac murmur, the most common finding, was observed in 16 (57.1%) newborns. Eight (28.6%) neonates were diagnosed with HF, 6 (21.4%) with cyanosis, 5 (17.9%) with arrhythmia, 5 (17.9%) with sepsis, and 3 (10.7%) with hypertension. No patient presented with acute pulmonary oedema. Sixteen (57.1%) cases required IMV, with an average duration of this ventilation technique of 10 days (range 1-36 days).

Medical treatment

During the acute phase, 12 (42.9%) newborns received treatment with inotropic agents (dobutamine or dopamine), 10 (35.7%) with vasopressors (dopamine or epinephrine), 11 (39.3%) with diuretic agents (furosemide or spironolactone), and 5 (17.9%) with afterload-reducing agents (milrinone or levosimendan). No neonate received preload- and afterload-reducing agents (**Tab. 2**). Two newborns were placed on a heart transplant waiting list. Both infants were transplanted at 2 and 8 months of age, respectively.

In terms of long-term and general management medication, 11 (39.3%) patients were treated with diuretics (furosemide or spironolactone), 11 (39.3%) with beta-blockers (propranolol or labetalol), 8 (28.6%) with ACEIs (captopril), 1 (3.6%) with anticoagulants (enoxaparin) and 1 (3.6%) with antiarrhythmics (amiodarone). No neonate was treated with digoxin.

Complications, evolution and outcome during the NICU stay

In the matter of complications, 3 neonates developed congestive HF, and another had an SCD event. No thromboembolic events were reported.

Neonates stayed at the NICU for an average of 18 days (range 1-78 days) before being discharged (**Tab. 3**).

Table 1. Demographic features and clinical presentation in 28 patients with cardiomyopathy (CM).

Demographic and clinical data		Primary CM			Secondary CM	All
		HCM	DCM	Tachy-CM		
Number of patients, n (%)		16 (57.1)	8 (28.6)	2 (7.1)	2 (7.1)	28 (100)
Sex	Male, n (%)	9 (56.3)	6 (75)	1 (50)	1 (50)	17 (60.7)
	Female, n (%)	7 (43.8)	2 (25)	1 (50)	1 (50)	11 (39.3)
Age at diagnosis (days), median (range)		3 (1-26)	3.5 (1-16)	15 (11-19)	19 (13-25)	5.5 (1-26)
Presenting signs/ symptoms	HF, n (%)	3 (18.8)	3 (37.5)	0 (0)	2 (100)	8 (28.6)
	Acute pulmonary edema, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Arrhythmia, n (%)	1 (6.3)	2 (25)	2 (100)	0 (0)	5 (17.9)
	Arterial hypertension, n (%)	1 (6.3)	1 (12.5)	0 (0)	1 (50)	3 (10.7)
	Cardiac murmur, n (%)	12 (75)	3 (37.5)	0 (0)	1 (50)	16 (57.1)
	Cyanosis, n (%)	4 (25)	1 (12.5)	1 (50)	0 (0)	6 (21.4)
	Sepsis, n (%)	4 (25)	1 (12.5)	0 (0)	0 (0)	5 (17.9)

CM: cardiomyopathy; HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; Tachy-CM: tachycardia-induced cardiomyopathy; HF: heart failure.

Table 2. Prescribed medication during neonates stay at the Neonatal Intensive Care Unit (NICU).

Medication during NICU stay	Primary CM			Secondary CM	All
	HCM	DCM	Tachy-CM		
Inotropic agents, n (%)	6 (37.5)	4 (50)	0 (0)	2 (100)	12 (42.9)
Diuretics, n (%)	3 (18.8)	5 (62.5)	1 (50)	2 (100)	11 (39.3)
Afterload-reducing agents, n (%)	1 (6.3)	3 (37.5)	0 (0)	1 (50)	5 (17.9)
Preload- and afterload-reducing agents, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vasopressors, n (%)	5 (31.3)	4 (50)	0 (0)	1 (50)	10 (35.7)
ACEIs, n (%)	2 (12.5)	4 (50)	0 (0)	2 (100)	8 (28.6)
Beta-blockers, n (%)	8 (50)	0 (0)	2 (100)	1 (50)	11 (39.3)
Digoxin, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anticoagulation, n (%)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (3.6)
Antiarrhythmics, n (%)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (3.6)

CM: cardiomyopathy; HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; Tachy-CM: tachycardia-induced cardiomyopathy; ACEIs: angiotensin-converting enzyme inhibitors.

Table 3. Patients' outcome and destination data.

Outcome and destination data		Primary CM			Secondary CM	All
		HCM	DCM	Tachy-CM		
Length of hospital stay (days), median (range)		9.50 (1-41)	21 (3-78)	7.50 (5-10)	20.50 (6-35)	10.50 (1-78)
Clinical state at discharge	Improved, n (%)	11 (68.8)	6 (75)	2 (100)	2 (100)	21 (75)
	Same state, n (%)	1 (6.3)	1 (12.5)	0 (0)	0 (0)	2 (7.1)
	Worsened, n (%)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (3.6)
	Deceased, n (%)	4 (25)	0 (0)	0 (0)	0 (0)	4 (14.3)
Destination [a]	Home, n (%)	2 (16.7)	2 (25)	1 (50)	0 (0)	5 (20.8)
	Pediatric ward, n (%)	8 (66.7)	4 (50)	1 (50)	1 (50)	14 (58.3)
	Other hospital, n (%)	2 (16.7)	2 (25)	0 (0)	1 (50)	5 (20.8)

CM: cardiomyopathy; HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; Tachy-CM: tachycardia-induced cardiomyopathy.
[a] Excluding deceased neonates.

Concerning the clinical state at the discharge date, 21 (75%) newborns improved during hospitalisation, 2 (7.1%) remained in the same state, and only 1 (3.6%) worsened his condition. However, 4 (14.3%) of the selected newborns died during the NICU stay. Thus, 24 neonates were alive at discharge. There were 14 (58.3%) admissions to the CHUSJ's pediatric ward, 5 (20.8%) transferences to other hospitals and 5 (20.8%) discharges home.

Prescribed medication at discharge

Newborns were prescribed with beta-blockers and diuretics (39.1%, each); antibiotics (30.4%); ACEIs and iron supplements (26.1%, each); antiplatelets, antiarrhythmics, anticoagulants, CCTs and paracetamol (13%, each); PPI and domperidone (8.7%, each); and anticholinergic (4.3%). All newborns were prescribed vitamins. One neonate was discharged without the need for any further outpatient medication. More than 90% of the newborns were prescribed more than one medicine at discharge.

Discussion

This report gives detailed information on the type, aetiology, clinical presentation, medical treatments, arise of complications, and outcome of CM in 28 newborns.

At CHUSJ, the prevalence of CM in neonates admitted to the NICU was 0.03%.

Our data shows that HCM was the most common type, followed by DCM. Most literature does not support our findings, considering DCM more frequently diagnosed than HCM [4, 7, 10, 13, 17], excepting one study that affirms that DCM is generally of later age presentation and rare during the neonatal period [14]. Withal, there are scarce studies approaching neonates and infants with CM [17]. Thus, little published data is available to validate our results, since most CM research portraits adults.

In our study, more than 92% of the neonates were diagnosed with primary forms of CM, and the remaining cases with secondary CMs. The available literature on the subject states that neonatal presentation of primary CMs is not frequent [14]. Furthermore, it also declares that secondary CMs may arise during the neonatal period, depending on the severity of the underlying cause [14].

Fourteen (58.33%) of the 24 cases of HCM and DCM were classified as idiopathic. Similar data has been published in several studies [10, 17]. Of the remaining 10 cases (**Fig. 2**), 8 were HCM and 2 were DCM. Malformation syndromes (3 cases) and inborn metabolic errors (2 cases) were the most common causes in the HCM subgroup. One case of familiar isolated CM was detected in that subgroup as well. A case of inborn metabolic error was found among the remaining cases of DCM.

More than 60% of the neonates included in the study group were male, which is in agreement with other series in the literature [6, 10, 17]. Male predominance is usually seen in HCM patients [17, 18], similarly to what we found in this study. The vast majority of DCM cases were established in male patients. Studies suggest that both genders are equally affected by this CM, with slightly more male individuals diagnosed in some reviews [13]. However, at least two studies did not support

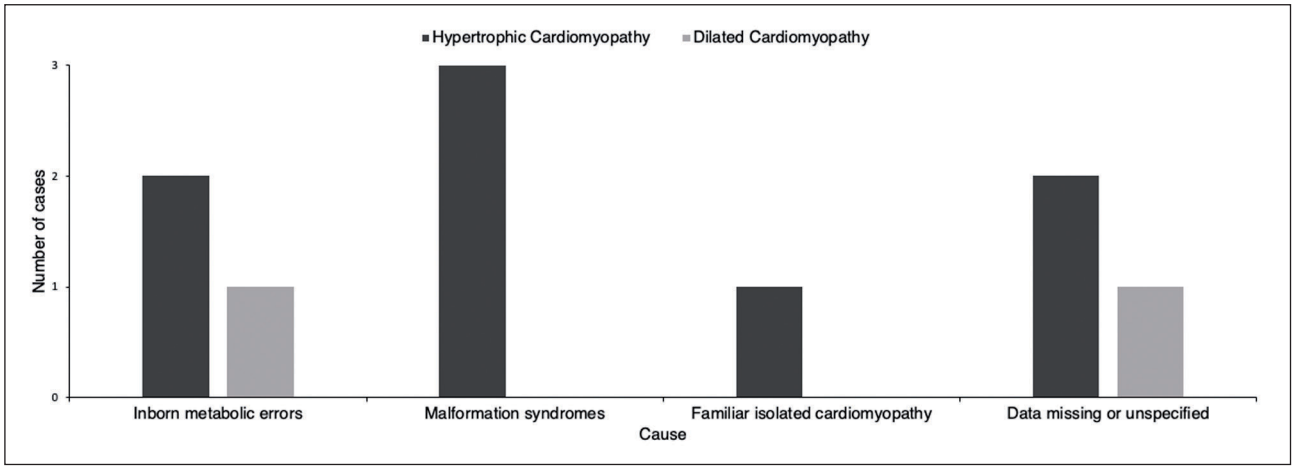

Figure 2. Primary causes of 8 cases of hypertrophic cardiomyopathy (HCM) and 2 cases of dilated cardiomyopathy (DCM).

this statement, as they showed female to be the dominant sex in DCM [7, 17].

Neonates' median age at diagnosis was 3 days (range 1-26 days) of life in HCM and 3.5 days (range 1-16 days) in DCM. These results are not concordant with data from two reports on CMs in infants, one of which also included neonates. In those reports, DCM's median age at diagnosis was inferior to the HCM's [10, 17]. Differences found between our results and published data could possibly be explained by the inclusion of an infants' group in the study population. Further studies analysing CMs exclusively in neonates are needed.

Glucocorticoids, such as dexamethasone or betamethasone, are extensively used in preterm newborns as prophylaxis and treatment of pulmonary conditions [19]. We found a case report that describes HCM in a preterm newborn after a single dose of dexamethasone, with spontaneous reversibility of the echocardiographic hypertrophic findings within 4 weeks [19]. Furthermore, another study showed that even short and low dose courses of dexamethasone therapy within the first 96 hours of life might produce clinically significant adverse cardiac effects, like ventricular myocardial hypertrophy [20]. Thus, awareness should be brought up to the fact that risks and benefits of corticoid use in preterm newborns must be weighted, as there is a plausible additional risk of HCM [19]. Even in our small dimensioned study, we were able to identify 3 premature newborns with a history of prior prenatal exposure to corticoids. Two of the preterm neonates developed HCM in the context of malformation syndromes, and during the NICU stay, 1 died and another improved. It is possible that corticotherapy was an underlying contributing minor factor for the occurrence of these HCM cases. The remaining preterm newborn developed DCM. We also found 1 case of a term neonate who developed HCM secondarily to corticotherapy.

According to a single centre study, more than 50% of neonates with CM present with a systolic murmur at the time of diagnosis [17]. Our results support this assertion, as there were 16/28 patients with a cardiac murmur at presentation, being the most commonly identified clinical finding. In HCM patients, this clinical finding is frequently a presentation sign [1, 4, 15], with some studies stating that it is the most commonly diagnosed one [14, 18]. Our findings are consistent with that information.

Less than 30% of all selected neonates had HF symptoms at diagnosis. However, this is not endorsed by available data [17]. HF was more frequently found in the DCM subgroup, similarly to what it is described in some reports [3, 17]. Furthermore, it is an unusual symptom in HCM patients, with less than 20% presenting it, as corroborated by another study [1].

All newborns who presented with cyanosis had either patent ductus arteriosus, pulmonary stenosis or right-to-left intracardiac shunt as an underlying pathology.

In our study, only a quarter of the newborns diagnosed with DCM presented with arrhythmia, which is consistent with published data [15]. All neonates with Tachy-CM were arrhythmic at presentation.

Although arterial hypertension has been described as present in nearly half of all HCM patients [16], only 1 case was observed in our HCM subgroup.

None of the neonates included in our study presented with acute pulmonary oedema. However, it has been reported as a frequent presentation sign in DCM patients [15].

Almost 20% of the newborns had sepsis as the inaugural diagnosis. It is quite common for cardiac disorders only to be established after complementary diagnostic exams fail to corroborate the presumed sepsis diagnosis or resuscitative attempts fall short of improving the child's condition [1].

All cases of HCM showed left ventricular hypertrophy (LVH) in echocardiographic findings, confirming LVH as a hallmark of this diagnosis [3, 16]. Left atrial enlargement (LAE) is an imagiologic aspect usually seen in DCM patients [13] and was found in 5/8 newborns included in our study. The presence of LAE may also be a clinical clue to the presence of HCM [16] and was detected in 1/16 patients of that subgroup. Patients with HCM commonly develop mild to moderate pulmonary hypertension as a result of elevated left atrial pressure [21], finding present in 12.5% of our HCM newborns. A quarter of DCM neonates presented with pulmonary hypertension, which has been proved to be an independent predictor of mortality in this subgroup of patients [22].

Medical treatment varies slightly according to the CM subtype, but it is grossly similar, irrespective of its aetiology.

In general, HCM's pharmacological therapy aims symptom reduction [4, 14, 16] and survival

prolongation [14]. Beta-blockers are the cornerstone of HCM's therapeutic approach [4, 14, 16] and in neonates, the preferred initial beta receptor antagonist is oral propranolol [4]. All 50% of the neonates with HCM medicated with a beta-blocker were given specifically propranolol. Inotropic agents such as dopamine and dobutamine as well as vasopressors like epinephrine should be carefully used in these patients [14]. Each of these agents was administered in 30-40% of all HCM neonates. Prescription of diuretics occurred in less than a fifth of these cases, which could be explained by the fact that its use is seen as counterproductive due to its size reduction effect on the left ventricular chamber size [1, 14, 15].

General therapy of HF applies to all individuals with DCM [15]. In this subgroup, as opposed to HCM patients, disease management is done with resource to inotropes, diuretics [1, 4, 13, 14] and vasodilators, particularly ACEIs [1, 13, 14], the latter being considered as first-line therapy for children and infants with CM [15]. Afterload-reducing agents also have a role in the treatment of these patients [14]. In our study, more than 60% of DCM neonates were prescribed with diuretics. Inotropic agents and ACEIs were administered to half of this subgroup. Afterload-reducing agents were given to 3/8 newborns. Beta-blockers are, however, rarely used as pharmacological support in DCM's acute states [1, 4, 15].

Tachy-CM's approach usually starts by treating the underlying arrhythmia, and the most common first choice are beta-blockers [8, 23]. Such *modus operandi* is in keeping with our results.

Concerning secondary CM, its management is highly variable, since it is based on the correction of underlying metabolic or genetic conditions [14].

Unsuccessful management of CMs can lead to the development of critical situations, such as severe HF, SCD, arrhythmia and thromboembolic events [4, 13, 14, 24, 25]. Congestive HF was the most commonly diagnosed complication in our study, and no thromboembolic events were registered.

Regarding SCD, studies suggest a remarkably low incidence in CM patients [17], occurring in less than 1.5% of all children listed for heart transplant [26]. According to available data of several studies, SCD in pediatric patients with CM is kept, in general, at an incidence of circa 5-5.5% [27]. This complication is predominant in adolescents and young adults with HCM [1] and is related to most death outcomes in this subgroup [15]. The only SCD registered in our study was of an HCM patient.

Several studies on CMs' outcome have been developed. However, most of them were conducted on children and adults. CM in neonates and infants still presents sparse data, and its natural history evolution is not yet well described [15]. There seems to be a tendency for worse survival in patients who present with CM at a younger age, such as the neonatal period [1, 6, 13, 16, 18]. There is, nonetheless, at least one study in which age at presentation did not influence the outcome [17]. At the same time, long-term recovery seems to be higher in infants when compared to older patients [15].

Three-quarters of the selected newborns improved their state during the NICU stay, and only 4 deaths occurred. Of those who ameliorated, 11 had HCM, 6 had DCM, 2 had Tachy-CM, and other 2 had secondary CM.

Studies suggest that in children with DCM, long-term outcome follows a "rule of thirds", in which a 1/3 improve, a 1/3 remain in the same chronic HF state and a 1/3 deteriorate their cardiac function and die [1, 13, 15]. Our findings, nevertheless, do not support this rule, since 75% of DCM patients improved their state.

More than 50% of the neonates who were alive at discharge from the NICU were admitted to the CHUSJ's pediatric ward, with a minority being either transferred to another hospital or discharged home.

This study was carried out in a level III NICU, a referral centre for maternal and neonatal pathology, which we consider to be its main strength.

Nevertheless, this study was marked by some limitations, such as being retrospective and observational in design with a relatively small sample size. Furthermore, since it was conducted in a single centre, our results cannot be generalised.

Ultimately, it is recognised that more prospective and multicentre studies are needed to evaluate these patients and to include them in a global database to better understand this rare neonatal pathology.

Conclusion

In summary, NCMs, although rare, are severe diseases that require critical intensive care management. At our reference centre, 0.03% of

all admissions to the NICU were diagnosed with a CM. The majority of cases were classified as idiopathic primary CMs.

Unspecific symptoms characterise clinical presentation and, thus, multidisciplinary (neonatology, cardiology, genetics, metabolic disease and endocrinology) approach is mandatory, since several rare aetiologies may manifest inaugurally as an NCM.

More prospective and multicentre studies are needed to evaluate these patients and to include them in a global database to better understand this rare neonatal pathology.

Declaration of interest

The Authors report no conflict of interests. The Authors received no financial support for the research, authorship, and/or publication of this article.

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